ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Evolving Treatments in Acute Myeloid Leukemia

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H&O Could you give some background on acute myeloid leukemia (AML)?

GR AML is the most common acute leukemia in adults. The median age of diagnosis is late 60s to early 70s, and there is some male-to-female predominance. There are approximately 13,000 new cases a year and 10,000 deaths a year. Unfortunately, most patients with AML still die of the disease.

Environmental factors, genetic abnormalities, and other benign hematologic diseases have been associated with increased risk for AML. We also know that AML risk is associated with previous chemotherapy and radiation exposure, so as people live longer with other types of cancers, it is possible that we will see an increase in AML cases.

H&O How does AML prognosis compare with other hematologic malignancies?

GR A recent survey by Sant and colleagues was published in the *Lancet Oncology* describing hematologic malignancies in Europe from 1997 to 2008, as well as incidence and outcomes. Compared with others, AML carries a poor prognosis and has one of the lowest survival rates. Looking at prognosis divided by age, we see that although there have been small advances among the younger patients, the older patients with AML continue to have a poor prognosis.

Although it is technically true that all of the hematologic malignancies showed statistical improvements in overall survival, in AML this improvement was only from 12.8% to 14.2%, highlighting the fact that statistical significance is not necessarily clinical significance.

Not all myeloid diseases have a poor prognosis. For example, acute promyelocytic leukemia and chronic myeloid leukemia have had the most improvement of any hematologic malignancy, with greater than 90% 10-year overall survival for selected patients. These excellent outcomes are attributable to improved understanding of the underlying disease pathophysiology and the use of highly effective therapies (ie tyrosine kinase inhibitors, all-trans retinoic acid, and arsenic trioxide).

H&O What is the current frontline treatment for AML?

GR The mainstay of treatment in AML is still cytarabine, a chemotherapeutic agent. The first paper using cytarabine, published in 1968 in *Blood,* called it "useful." Even 40 years later, it is probably the best drug that we have in AML.

In 1973, the first pilot study was performed using an infusion of cytarabine and daunorubicin, called "7+3 DNR 45" (ie, 7 days treatment with cytarabine plus 3 days with daunorubicin at 45 mg/m^2). Using this regimen produced a complete response rate of 56% in AML, which still makes it the regimen to beat.

There have since been modifications to classic 7+3 over the years, but few significant improvements. In 2009, Fernandez and colleagues published a randomized comparison of daunorubicin dosage at 45 mg/m^2 vs 90 mg/m^2, and found that 90 mg/m^2 is better. From this study, we better understand how to use our best therapy, 7+3, and this has resulted in a survival benefit for selected, younger AML patients.

Lowenberg and colleagues investigated the feasibility of daunorubicin intensification in older patients and found that it can be administered without significant additional morbidity or mortality, but without improvement in overall survival for patients older than 65 years.

H&O Are there any studies on additive therapies for 7+3?

GR There have been many attempts to improve 7+3, with very little success. Buchner and coauthors compiled results—published in the *Journal of Clinical Oncology* in 2012—from multiple investigational trials in Europe that sought to improve 7+3 by using additional drugs along with cytarabine plus daunorubicin. The standard comparator they used was induction with 3 days of daunorubicin 60 mg/m^2, 7 days of cytarabine 100/m^2, and consolidation with 3 courses of high-dose cytarabine (HIDAC).

The studies investigated various possible modifications to 7+3, including addition of etoposide or thioguanine, administration of 2 induction cycles, fractionated or continuous HIDAC for induction and consolidation, and autologous vs allogeneic stem cell transplant. Unfortunately, none of these changes yielded significant improvement in patients; in fact, all the survival curves from the different trials are superimposable. Therefore, one may ask whether it might be "the triumph of hope over experience" to attempt further chemotherapy-based modification of 7+3. It is possible that we are not using the correct novel agents and/or that we are adding them at the wrong time during AML treatment.

Interestingly, there have been at least 2 modifications to standard induction that did appear to show some benefit. Cladribine was added to 7+3 and showed improved overall survival in a large randomized trial, but, for unclear reasons, this agent has not been adopted into standard practice. The addition of gemtuzumab ozogamicin has also shown benefit in selected clinical trials, but it is not commercially available at this time.

There are other agents under evaluation as potential partners for 7+3, including decitabine, azacitidine, and temsirolimus (Torisel, Wyeth). My group at Weill Cornell conducted a study using decitabine as a "priming regimen" administered prior to 7+3, and this regimen has been adopted as the investigational arm in an ongoing randomized trial vs 7+3. I hope that the outcome of this study will be a win for the investigational arm. The bottom line is that, 40 years later, 7+3 is still the regimen to beat.

H&O Are there any chemotherapeutic agents in clinical trials to replace cytarabine?

GR There is clofarabine, which currently is approved for use in relapsed or refractory acute lymphoblastic leukemia. Clinical trials have shown that it is effective in AML when used on its own, but a regimen that shows improved efficacy over cytarabine has not been determined.

There is also CPX-351, a formulation that holds cytarabine and daunorubicin in a fixed 5-to-1 molar ratio. Recent trials of CPX-351—published in *Blood* in 2014 by Lancet and colleagues—showed a benefit in overall survival for a very difficult-to-treat population of secondary AML patients. A randomized trial of CPX-351 versus 7+3 is ongoing.

H&O Have there been any improvements in treatments using low-dose cytarabine?

GR The current, standard low-intensity regimen using 10 or 14 days of low-dose, subcutaneous cytarabine (LDAC) has been used for older, frail AML patients for more than 30 years. An ongoing, multi-arm trial in United Kingdom is serially randomizing an assortment of novel compounds against standard LDAC. Several agents have already been tried, including vosaroxin, clofarabine, gemtuzumab, tipifarnib, and arsenic trioxide. These agents looked promising in combination with LDAC in single-arm studies, but failed to significantly improve survival in the randomized trial.

The good news is that there continue to be novel agents on the horizon that can be combined with and/or compared with LDAC. Potential competitors include volasertib, a polo-like kinase 1 (PLK-1) inhibitor; SGN-33, a novel antibody-drug conjugate; and SGI-110, a second-generation hypomethylator. Decitabine has also been compared with LDAC by Kantarjian and colleagues, and the data were sufficient to convince the European Medicines Agency, but not the US Food and Drug Administration, that decitabine is an effective low-intensity treatment for AML. Several studies have found that 10-day decitabine is especially effective, with response rates of 40% to 47%. There are also many ongoing trials of combinations of decitabine and azacitidine in AML that have solid scientific rationale behind using the combination. These data are anxiously awaited.

H&O Are there any new treatments for relapsed AML?

GR Unfortunately, we do not have any breakthroughs for relapsed AML. Elacytarabine, which is a liposomal formulation of cytarabine, failed to show a benefit in a trial with relapsed patients that we published in 2014 in the *Journal of Clinical Oncology*. This study was interesting, because it used investigator's choice as the control regimen, and it resoundingly showed that all the regimens chosen for relapsed disease are equally ineffective.

Vosaroxin, a topoisomerase inhibitor, did not meet its endpoint in a recent trial (NCT01191801) studying

relapsed disease, but it still is associated with a high complete response rate. Therefore, this drug may be useful in the future, when we determine how to use it optimally.

H&O What are the new targets for mechanism-based therapies?

GR Multiple mutations have been characterized in AML, including mutations affecting proliferation (eg, receptor tyrosine kinases and signal transduction proteins), differentiation, apoptosis, epigenetic regulation, and the spliceosome. We have found aberrant histone modifications, dysregulated DNA methylation, and metabolic alterations. There are also quiescent leukemic stem cells that are not chemotherapy-sensitive. Although the mechanisms of the disease are much better understood than before, all of these alterations combine to create a complicated mechanism of action. But overall, we are investigating epigenetics, targeted therapies, and personalized medicine. Hopefully, we will soon be on the way to improved therapeutic options.

H&O Are there any promising treatment strategies other than chemotherapy?

GR Mutation-targeted strategies, FMS-like receptor tyrosine kinase-3 (Flt3) inhibitors, and isocitrate dehydrogenase (IDH) 1 and 2 inhibitors all are extremely promising. One question is whether these can improve upon previous therapies. Another major concern is whether we are putting selective pressure on 1 clone and thereby creating more mutations that are resistant to therapy.

To avoid this problem, it is possible to target the machinery instead of the mutation. One interesting example is bromodomain inhibition, which reduces the transcription of genes associated with cancer cell proliferation and survival. This strategy is of particular interest because it is a way to slow propagation of AML cells without focusing only on a single isolated mutation.

Immunotherapy is also a promising novel treatment area, especially adoptive cell transfer (ACT). ACT uses the patient's own T cells, which are modified to express chimeric antigen receptors (CARs) that target a specific antigen on the tumor cells. This is a promising new therapy that could potentially be useful in AML.

Suggested Readings

Büchner T, Schlenk RF, Schaich M, et al. Acute Myeloid Leukemia (AML): different treatment strategies versus a common standard arm—combined prospective analysis by the German AML Intergroup. *J Clin Oncol*. 2012;30(29):3604-3610.

Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259.

Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30(21):2670-2677.

Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123(21):3239-3246.

Löwenberg B, Ossenkoppele GJ, van Putten W, et al; Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON); German AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.

Ritchie EK, Feldman EJ, Christos PJ, et al. Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia. *Leuk Lymphoma*. 2013;54(9):2003-2007.

Roboz GJ. Current treatment of acute myeloid leukemia. *Curr Opin Oncol*. 2012;24(6):711-719.

Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. *J Clin Oncol*. 2014;32(18):1919-1926.

Roboz GJ, Wissa U, Ritchie EK, et al. Are low-intensity induction strategies better for older patients with acute myeloid leukemia? *Leuk Res*. 2012;36(4):407-412.

Sant M, Minicozzi P, Mounier M, et al; EUROCARE-5 Working Group. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. *Lancet Oncol*. 2014;15(9):931-942.